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Results and Prospects of Scientific Cooperation between the U.S.S.R. and the U.S. on the Problem of Environmental Health

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Cooperation on the problem of environmental health developed during 1973–74 in conjunction with the program signed in the United States in January, 1973 by the program coordinators of both countries and approved by the Second Session of the Joint Soviet–American Commission on Cooperation in the Field of Medicine and Public Health (March 1973).

Up to the signing of the Intergovernmental Agreement on Cooperation between the U.S.S.R. and the U.S., the development of environmental research on problems related to the chemical pollution of the environment proceeded independently in each country. Contacts between scientists in this area did not exist, and the exchange of scientific information was minimal. This, along with the diversity of the methods used for solving problems associated with protecting the environment from pollution, resulted in a diversity of approaches towards the solution of this problem on the part of Soviet and American scientists.

During the development of the first program on Soviet–American research in environmental health, the two countries agreed jointly to determine and verify the basic principles, criteria, and methods used for evaluating the biological action of chemical pollutants. This is, of course, basic to the establishment of environmental standards and the development of measures for environmental protection.

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The problems chosen for joint research are methodological in nature. The scientific subject matter has been combined into three problem areas: methodological basis for the assessment of the biological effect of inhaled chemicals, methodological basis for the assessment of the biological effect of orally introduced chemicals, and scientific basis for the assessment of the complex biological effects of chemical substances. The necessity for uniting the efforts of scientists of various countries is justified by the global nature of the problem, the inability of any single country to solve the entire problem, and by the rapidly mounting cost of scientific research.

The joining of forces by the U.S.S.R. and the U.S. to deal with the problem of environmental health is the result of the joint drive by various countries towards the solution of problems in common which encompass the entire population of the planet. The fact that the United States and the Soviet Union have the most powerful industrial and scientific potential gives hope that the joint contribution of these countries to the solution of the problem will be significant. The practical realization of scientifically based measures for improving the environment requires a step-by-step solution. Scientific research must serve as the real basis for the development of governmental legislation of each country and, if necessary, also for intergovernmental legislation.

Research directed towards protecting the public from possible untoward environmental effects is

one of the most important problems, in my opinion, in the area of environmental health. The research of Soviet hygienists is directed towards the establishment of standards for allowable levels of environmental pollution in air, water, and soil. These standards serve as the basis for the control of environmental pollution by the State Sanitation Service.

In the development of cooperation on this problem during the past two years, direct contacts were established between the Soviet and American scientific topic leaders, detailed programs have been worked out, and joint experimental research conducted. At present there is a regular exchange of scientific information and literature and an exchange of specialists. Nineteen American scientists visited the U.S.S.R. and 15 Soviet scientists visited the United States during the course of 1973–74.

In the first problem area, new important results of mutual interest have been obtained.

Research on quantitative relationships of dose–time–effect for biological prediction is going well, in particular work on the evaluation of the biological effect of atmospheric pollutants. This involves the accelerated substantiation of health standards for harmful substances in the atmosphere and the evaluation of their intermittent effect.

The prediction of biologic effects (in particular, threshold effects) can be based on the study of the concentration–time relationship. In order to derive a quantitative expression for such a relationship, experiments are being conducted in the U.S.S.R. on animals to determine the onset time of given toxic effects (prostration and death of 50% of the mice, along with changes in some of the physiological and biochemical indices) with respect to the continuous and discontinuous inhalation of a series of organic substances (nonelectrolytes) at various concentrations.

The concentration–time relationship, both with respect to acute toxicity parameters and physiological and biochemical indices, can be expressed by a straight line relationship on a log - log plot with respect to the continuous inhalation of the indicated substances. This is promising with respect to the prediction of toxic effects on the basis of short-term experiments with subsequent exprapolation to longer periods. Nevertheless, the possibility of such extrapolation at present is limited to a period of 3–4 months, i.e., to those periods of time covered by the study.

The goal of future research is continued study of the concentration–time relationhip for longer experimental periods (7–8 months) to establish the nature of this relationship for the inhalation of inorganic substances, for example, sulfur dioxide.

Our American colleagues have been studying the dose–time relationship and developing approaches for evaluating the intermittent action of chemical substances with respect to their inhalation entrance into the organism. As opposed to Soviet specialists who are evaluating the state of the total (integral) reactions of an organism, American scientists are studying primarily the local reactions of lung tissue with respect to the effect of atmospheric pollutants including the combined action of chemical and biological factors.

Mutually supplementary research can be developed for this topic area. The results of such research will aid in the solution of the paramount problem of predicting biological effects.

Significant progress has been achieved on prediction of the biological effect of chemical substances on the basis of their chemical structure. In the U.S.S.R. an attempt was made, using 25 benzene derivatives as examples, to establish a relationship between the biological effect thresholds of the given substances, their chemical structure, and the basic physicochemical properties. The result of this was the development of computational formulas which make it possible to make a preliminary prediction of the reflex action threshold, not only for the derivatives of benzene but also for a series of organic substances (molecular weight from 30 to 300, boiling temperature 37–315°C) without the need for long-term experimental study of these substances.

Joint work on the mechanism and indices of harmful effects of certain chemical substances on the central nervous system should be continued, including a comparative evaluation of the various methods of behavioral toxicology and functional electroencephalography which are accepted in our countries using, for example, the toxic effect of carbon bisulfide on the organism.

American specialists studied the behavioral toxicology of carbon bisulfide on pigeons and with the electrical activity of the brain of primates. Soviet specialists studied the behavioral reactions of rats, the electrical activity of the brains of rabbits, and the motor activity of man.

Soviet specialists determined the most sensitive structures of the brain and the time necessary for the action of a toxic substance on the central nervous system. Sensitization processes were studied.

Soviet and American specialists conducted neurochemical studies on the brain which made it possible to obtain data on the role of dopamine-beta-hydroxylase (U.S.) and neuramic acid

(U.S.S.R.) in the reaction of the central nervous system to the effect of carbon bisulfide.

Thus the exchange of various methodological approaches used in both countries and the establishment of a series of important biological regularities associated with the toxic effect of carbon bisulfide on the organism are the result of cooperation within the framework of this topic.

Research will be continued on the effect of other chemical substances on the evoked potentials of the human brain and on the neurochemistry of the brain of experimental animals.

Appreciable progress has been achieved in joint research on the second problem area.

Of interest is the development of research on the general principles of toxicological dynamics of chemicals to establish procedures in chronic experiments, such as duration of the experiment, frequency and technique of oral introduction, extrapolation from animals to man, and prediction of subthreshold concentrations on the basis of the dose–effect relationship. This research is directed towards the development of a methodological scheme for predicting safe toxic levels for man (maximally permissible concentration values) on the basis of the results of intoxication modeling in animal experiments.

Soviet specialists have improved the computational method of extrapolation and studied the levels of rectilinear regression. This method is more accurate than a series of other methods for extrapolation. In order to increase the reliability of extrapolation of toxicologic data, errors involved in the carry over of experimental data to the population as a whole must be considered as well as errors incurred in the carry over of experimental data to the "average" man.

A computational method was used to predict the toxic effect of chemical substances for man only based on the data of short-term tests. The problem of extrapolating the results of the experimental study of long-term effects (particularly gonadotropic and mutagenic) requires further research.

The gonadotropic effect is characteristic of the action of cadmium and boron on animals. The relationship between the toxic and gonadotropic effects of these substances with respect to the various species of laboratory animals must be determined. To acquire the necessary material, it is advisable to conduct joint research on the evaluation of toxic and gonadotropic properties of other chemical compounds, for example aluminum and nitrites. Further study is also required to prefect the theory of intoxication modeling and to develop criteria and principles for model selection in experiments.

American research compared the symptoms of intoxication in man and laboratory animals with respect to the study of the biologic effects of anticancer preparations. This type of methodological approach is original and useful for the objective selection of experimental models in toxicological tests. The data obtained show that it is possible in most cases reliably to predict intoxication symptoms in man (with the exception of skin damage) from the results of experiments on animals.

Useful experience has been accumulated in studies of cadmium and boron in which the conditions for conducting the tests had been agreed upon beforehand. The same experimental model was used, and the same doses were tested, but different research methods used: toxicologic tests, functional methods for studying spermatogenesis (U.S.S.R.), and biochemical and morphological methods for evaluating gonad function (U.S.). The data obtained from the study of cadmium and boron can be used in establishing health standards of these substances in water, i.e., for the further improvement of the national standards in the U.S.S.R. and the U.S. with respect to drinking water quality and water reservoir quality.

The development of research on the relationship of toxicity to physicochemical properties of compounds may be very promising. In the U.S.S.R., work has been conducted on the development of mathematical methods, the derivation of regression formulas for a series of chemical compound groups (phosphorooganic, chloroorganic), and development of a rapid experimental method (short-term, one-month test) for phosphoroorganic compounds to determine threshold and nonactive chronic toxicity levels of substances. This method is laborious relative to existing methods for establishing health standards for chemical substances in water. Analysis of the material shows that the predicted values are quite reliable (the divergence from experimental values is 2–5 times) while those methods which use the toxicologic parameters of substances (LD_{50} LC_{50}, MPC) are promising for prediction. Very promising research on this topic was conducted in the United States. This included the development of methods of prediction based on interactions with proteins and lipids (phospholipids), American scientists studying the nature of the activity of chemical substances with respect to the basic components of the cell. These prediction methods are simple to use and serve as a

basis for constructing models for the behavior of substances both in the organism and in the environment. A comparison of the various methods for predicting the toxic and nonactive levels of chemical compounds for an organism by using the phosphoroorganic compounds as an example makes it possible to utilize the most appropriate methods and to use them together for mutual verification. Further work can take the direction of the development by both countries of their own methods for predicting the toxicity parameters of substances with respect to other groups of chemical compounds (nitro compounds).

In accordance with the preliminary agreement, we deem it advisable to conclude joint research on development of more rapid methods of assessment of biological effects of chemical substances in 1974.

Research on the third problem area is going well.

Research on long-term effects of carcinogenic environmental chemical agents in the U.S.S.R. has determined basic regularities associated with the carcinogenic substance–organism interaction which is expressed by the dose–time–effect relationship. This was done by an experimental study of the carcinogenic effect of various doses of benzpyrene in the 0.005–25 mg range with intratracheal introduction and concurrent determination of morphological and histochemical particularities of tumor growth as a function of carcinogen dosage.

On the basis of these data, principles for extrapolating experimental data to man and methodological approaches towards the establishment of health standards for carcinogenic substances in atmospheric air were developed. At present a joint article is being prepared for publication.

Experiments were conducted in the U.S.S.R. during 1973 on the explanation of some methodological problems. These experiments made it possible to determine the dependence of the tumorgenic effect of the multiplicity of carcinogen introduction and to determine the optimal interval between individual introductions of large doses of benzpyrene.

In 1974 various doses of benzypyrene were given to experimental animals through the respiratory organs, through the gastrointestinal tract, and through the skin, individually and by two or three routes of administration.

During 1975, observations will be made of the experimental animals subjected to the above exposures, and the organs and tissues of the animals will be pathohistologically studied after the natural death of the animals.

It is assumed that these studies will make it possible to evaluate the role of various routes of administration of carcinogens into an organism and their interaction as concerns the development of the neoplastic process.

Cooperation on this topic made it possible to compare the methodological approaches used in both countries for estimating the risk of tumor occurrence due to the action of carcinogenic substances and on the basis of the critical evaluation of the methodological approaches, to recommend principles for environmental standards.

Research on the long-term effects of cocarcinogenic environmental chemical agents is concerned with the study of the interaction of carcinogens and other compounds (sulfur dioxide, phenol, oxides of nitrogen, and croton oil) which result in malignant tumors of the lungs.

During the last two years, studies have been carried out in the U.S.S.R. on the combined action of a carcinogen and phenol. The completion of this work is planned for 1975. The results of the work (particularly methodological approaches, and biochemical and physiological studies) have been sent to the United States in the form of reports and a national literature survey.

Further bilateral studies are most likely to be directed to investigation of the mechanism responsible for the biological action of such chemical cofactors in the blastomogenesis of the lungs, the determination of the significance of low concentration in cocarcinogenesis, and the testing of new chemical substances with respect to cocarcinogenesis.

In cooperative studies of assessment methods for combined and complex effects of pollutants with respect to their inhalation entrance, both countries have undertaken to solve one of the major problems in this area, i.e., study of the combined action of substances which have a unidirectional toxic action nature. The task of the research is general: the comparison of the effect of the action of a combination of substances at various concentration levels with respect to duration of various effects. Research in the U.S.S.R. has been concerned with the study of the action of three substances, individually and in combination, with narcotic and hepatotropic effects under subacute and acute experiment conditions. The research in the United States was begun only during the second half of

1974; nevertheless a positive feature is that agreement on the uniformity of the methodological approaches used in this research has been achieved. This is no small matter, because it makes possible comparison of research results and general conclusions.

Joint research is going well on the study of the complex effect of pesticides in relation to their movement through the environment. Soviet specialists have been conducting experimental studies on the possible embryotropic effect of phosphororganic pesticides, chlorophos (dipterex) and phthalophos (imidan), which would follow from the possible introduction of these pesticides into the organism with food, air and water. The development of these studies in the U.S.S.R. will take the direction of studying the effect of chlorophos resulting from the complex and simple entrance of this substance into an organism at various doses. Research in the United States is concerned with the experimental study of the gonadotoxic effect of these same substances.

As the result of the exchange, analysis and generalization of the data obtained, it becomes possible to select for implementation the most suitable and universal methods for determining the embryotoxic and gonadotropic properties of pesticides. It also makes possible an evaluation of the degree of danger which the substances studied present to the health of a population.

On positive evaluation of the overall development of cooperation on the problem of environmental health, it must be stated that scientific cooperation aids in the establishment of personal human contacts between the participants and makes it possible for scientists to know each other and understand each other better. This is also a very important result of our work in common.

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